**Elevator Pitch**

I am interested in understanding how much van der Waals packing is necessary for membrane proteins to fold. Membrane proteins are proteins that associate with lipid bilayers and are important for essential biological functions including cell-cell signaling and gene regulation (found in biological complexes like integrins, RTKs, …; interior and exterior of the cell). These proteins compose 25-30% of the human (various) genome, and represent more than half of all currently made drug targets against disease. Although this is the case, only around 2% of proteins found in the PDB are membrane proteins, demonstrating a gap in being able to characterize and understand membrane protein structure. My project focuses specifically on understanding the folding aspect of membrane proteins, or how these proteins properly fold into functional structures.

Membrane protein folding takes place in two distinct steps: First, the protein is translated by the ribosome and transported into the membrane by a protein known as a translocon. The second step of folding occurs after the entire protein has been inserted: As a result of hydrogen bonds, electrostatic interactions, and van der Waals packing, the individual parts of the protein associate into a stabilized structure. I am specifically interested in the second step of folding and characterizing the strength of van der Waals packing. Because van der Waals packing is an attraction between any atoms in close contact, it is an implicit force for folding to occur whether or not hydrogen bonding or electrostatic interactions are involved. Previous research has shown that disrupting packing within the core of membrane proteins leads to destabilization of the folded state. In addition, membrane protein design has demonstrated that optimization of packing interfaces between protein subunits can lead to stable structures. By combining these two methods into a dimeric model system that has been used to study the forces in folding previously, I will study how much van der Waals packing is necessary between protein subunits for stability.

Two-stage model: secondary structure forms, then tertiary and quarternary structure

Energetics based on sequence; holy grail for chemistry: protein folding problem, fundamemntal problem (how do these rapidly find it’s final state; as fundamental as understanding enzyme catalysis, how do proteins work; difficult to investigate the fact that van der Waals is important, so why haven’t we studied this basic research problem; critical problem at the core of membrane protein folding; by understanding it, go on to design and improve prediction)

Using well known computational design techniques, I aim to design sequences with structures that have an array of packing strength from weak to strong, where weak packing should result in weak dimerization and vice versa for strong packing. I will test these sequences and determine correlation between our expectation of dimerization by design and propensity to dimerize *in vivo*. Then, I will take a subset of these sequences and quantify the thermodynamic range of packing necessary for association *in vitro*. Overall, my research will determine how much van der Waals packing is necessary to provide stability to associated subunits of membrane proteins. With a better understanding of implicit van der Waals packing, further design may enable us to study how much other forces (hydrogen bonding, electrostatics, and lipid effects) contribute to membrane protein folding as well. By better understanding the forces that govern membrane protein folding, we may gain insight into how specific structural changes in a membrane protein may alter function. This is particularly important for understanding why misfolding of membrane protein structures can lead to disease phenotypes, such as cancer. With more knowledge of the impact of van der Waals packing on membrane protein folding, we will have a better understanding of how to predict and design structure, enabling more accurate design of drugs against proteins targets with uncharacterized structures.

Add more emphasis on the knowledge gap of folding: no chaperones (?); how much of the problem has been attempted? Are there membrane protein chaperones that we know for sure associate with second step of folding?

Point out that tertiary structural folding is still a large knowledge gap: How

Innovation: Being able to measure these is important and hasn’t been done

You can learn a lot about enzymes just by looking at kinetics; by understanding the parameters that make these reactions happen, we can get more information than structure gives us